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PCI OR CABG IN LEFT MAIN CORONARY ARTERY DISEASE: A COMPREHENSIVE META-ANALYSIS OF ADJUSTED OBSERVATIONAL STUDIES AND RANDOMIZED CONTROLLED TRIALS.

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Abbreviations list:

ULMCA (Unprotected Left Main Coronary Artery Disease); **PCI** (Percutaneous Coronary Intervention); **CABG** (Coronary Artery Bypass Graft); **RCTs** (randomized controlled trials); **NRCTs** (Non Randomized Controlled trials); **MI** (Myocardial infarction) ; **MACE** (major adverse cardiovascular events); **DES** (drug eluting stent).

ABSTRACT:

BACKGROUND. Treatment of patients with ULMCA (Unprotected Left Main Coronary Artery Disease) with Percutaneous Coronary Intervention (PCI) has been compared with Coronary Artery Bypass Graft (CABG), without conclusive results.

METHODS. All randomized controlled trials (RCTs) and observational studies with multivariate analysis comparing PCI and CABG for ULMCA were included. Major cardiovascular events (MACEs, composite of all-cause death, MI, definite or probable ST, target vessel revascularization and stroke) were the primary end points, while its single components the secondary ones, along with stent thrombosis, graft occlusion and in hospital death and stroke. Subgroup analyses were performed according to Syntax score.

RESULTS. 6 Randomized Controlled Trials (4717 patients) and 20 observational studies with multivariate adjustment (14597 patients) were included. After 5 (3-5.5) years, MACE rate was higher for PCI (OR 1.10, 95%CI 1.07-1.14), without difference in death, while more relevant risk of MI was due to observational studies. Coronary stenting increased risk of revascularization (OR 1.52:1.34-1.72). At meta-regression, performance of PCI was improved by use of intra-coronary imaging and worsened by first generation stents, while two arterial grafts increased benefit of CABG. For patients with Syntax score <22, MACE rates did not differ, while for higher values CABG reduced MACE due to lower risk of revascularization. Incidence of graft occlusion was 3.24% (2.25-4.23), while2.13% (1.28-2.98: all CI 95%) of patients. experienced stent thrombosis

CONCLUSION. Surgical revascularization reduces risk of revascularization for ULMCA patients, especially for those with Syntax Score>22, with a higher risk of in hospital death.

Intra-coronary imaging and use of arterial grafts improved performance of revascularization strategies.

INTRODUCTION:

The high risk related to stenosis of Unprotected Left Main Coronary Artery (ULMCA) and its negative prognostic impact is largely known. This condition is reported in about 6% of patients undergoing coronary angiography both for acute coronary syndromes as in stable angina(1).Coronary Artery Bypass Grafting (CABG) has long been considered the treatment of choice for ULMCA (2). Development of drug-eluting stents (DESs) and use of imaging techniques increased use of PCI (Percutaneous Coronary Intervention) with satisfactory results even at long term follow up (3,4). Some Randomized Controlled Trials (RCTs) compared PCI and CABG demonstrating similar results in terms of death, myocardial infarction, stroke with a benefit of CABG in terms of lower subsequent revascularization (5,6). Use of multiple arterial grafts and of new generation drug eluting stents have been advocated by cardiac surgeons and interventional cardiologists, respectively, as promising strategy in this field, but contrasting data have been recently provided (7,8). A recent meta-analysis based only on RCTs and including last published papers with newest DESs generation, confirmed similar efficacy between the two approaches except for higher repeated revascularization with PCI (9).Data from observational studies with multivariate adjustment may be of interest, in order to increase the body of evidence expanding the sample size from one side, and to test the reproducibility of RCTs results to real life patients, often excluded from RCTs (10).

Aim of this meta-analysis is to overcome the lack of clear scientific evidences by pooling data from available RCTs, propensity-score adjusted trials and studies performing Cox multivariate analysis.

METHODS:

The present study was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses statements (PRISMA) (11-15).Pubmed, Cochrane, and Google Scholar were searched for the following terms: “coronary artery bypass” and “coronary stenting” and “multi-vessels disease” and “left main disease” by 2 authors (MB and ODF). Citations were first screened independently by 2 reviewers (MI and FDA), with disagreements resolved by consensus. Inclusion criteria were (i) human studies, (ii) comparing PCI with CABG for LM revascularization, (iii) with a follow-up longer than three years and (iv)more than 50 included patients to avoid limited sample effect. In the case of duplicate reporting, the manuscript with the largest sample of patients was selected. By authors’ choice, papers not written in English were excluded from this analysis.

Data abstraction.

The following data were independently abstracted by 2 reviewers (MI and FDA) on pre-specified electronic forms, with disagreements resolved by consensus: authors, journal, year of publication, location of the study group, type of DES, baseline, angiographic and procedural features, kind of bypass graft, and definition of bleeding were collected. The corresponding authors of the relevant studies were queried to provide quantitative details

not available in the published manuscripts and were included in the project **(see appendix, web only).**

End points.

Major cardiovascular events (MACEs: composite of all-cause death, MI, definite or probable ST, target vessel revascularization [TVR]) was the primary end point, while its single components were the secondary ones, along with graft occlusion TLR (Target Lesion Revascularization) and in hospital death and stroke. Subgroup analyses for MACEs, death and revascularization were performed according to Syntax score. Meta-regression analysis was performed to evaluate impact of site of stenosis and of choice of strategies on revascularization.

Quality study evaluation.

The quality of included studies was independently appraised by 2 reviewers (MI and FDA), with disagreements resolved by consensus. For each randomized controlled trial, we evaluated the risk of bias (low, moderate, unclear, or high) for random-sequence generation, allocation concealment, blinding of patients and physicians, blinding during assessment of follow-up, incomplete outcome evaluation, and selective reporting, in keeping with the Cochrane Collaboration approach (See Appendix, **table S1-S2**, web only).

Statistical analysis.

Continuous variables are reported as mean (SD) or median (first and third quartile). Categorical variables are expressed as n (%). Statistical pooling for incidence estimates was performed according to a random-effect model with generic inverse-variance weighting, computing risk estimates with 95% confidence intervals (CIs), using RevMan 5.2 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). Small

study bias was appraised by graphical inspection of funnel plots. Meta-regression analysis was performed to assess the impact of baseline features on the primary end point with Comprehensive Meta-analysis software (trial version). Hypothesis testing for superiority was set at the 2-tailed 0.05 level. Hypothesis testing for statistical homogeneity was set at the 2-tailed 0.10 level and based on the Cochran Q test, with I2 values of 25%, 50%, and 75% representing mild, moderate, and severe heterogeneity, respectively.

Statistical methods and baseline and interventional variables included in the propensity score matching/multivariate analysis of observational studies are described in Appendix **table S6 A-B** (web only).

RESULTS

Studies selection and baseline features

A total of 2358 results emerged from the key research used. After an accurate analysis of title, abstract and, if necessary, full-text, 2332 works were excluded as they did not full-fill inclusion criteria previously stated. In particular, 2077 were ruled out because not pertinent, 34 were not in English, 95 results were editorials/case report/reviews, 50 were nor RCTs nor multivariate adjusted studies, 58 had an inadequate follow up (< 3 years), 2 studies excluded because of a small sample size (<50 patients). Of 42 results firstly selected, 16 were then judged as redundant since conducted among a population enrolled in larger trial. 26 papers were finally selected for the systematic review and meta-analysis, 6 Randomized Controlled Trials (RCTs) and 20 observational studies with multivariate adjustment or propensity score analysis (NRCTs) **(see appendix, web only)**. 19314 patients were included in the final analysis, of which 8501 treated with PCI and 10813 with CABG. 4717 patients were enrolled in RCTs (2360 in PCI group and 2357 in CABG group) and 14597 in NRCTs (6141 in PCI group and 8456 in CABG group, **see Figure nr. 1**).

Mean age of overall population was 64 ± 9 years; 26% were female, 64% were hypertensive, 32% were diabetic. Median syntax score was 26, while single-study Euroscore value and type are described in **Table S4A (web Appendix only)**. 12% of the patients had a single lesion of LM, while distal LM stenosis was reported in 65% of them (**see Tables 1 and 2 for overall data and Table S4-S5, web Appendix only, for specific single study data**).

Primary endpoint analysis

22 of the 26 included studies (6 RCTs including 4717 patients and 16 NRCTs for 13375 patients) evaluated the incidence of MACEs in the 2 groups (8055 patients for PCI group and 10037 for CABG group). After 5 (3-5.5) years, the overall incidence of events was higher in PCI group compared with CABG group (OR 1.10, 95%CI 1.07-1.14, p <0.01). This result was confirmed in both NRCTs (OR 1.11:1.07-1.16, p<0.00001), and RCTs subgroups (OR 1.07:1.01-1.14, p 0.03) **(see Figure 2 and S2 in web appendix)** and considering only studies not including revascularization in MACE definition **(see Figure S1 in web appendix)**

Secondary endpoints analysis

All the studies selected for the primary endpoint were also included in the analysis of death. According to death there was a not significant trend for higher incidence in CABG group in the general analysis (OR 0.94:0.89-1.00, p =0.05), with a neutral result in the subgroups (OR 0.92:0.78-1.07; p=0.27; and OR 0.95: 0.89-1.02; p=0.14 respectively for RCTs and NRCTs) **(see Figure 3, Panel A)**

All RCTs and 7 NRCTs (total patients 12129, 7412 from NRCTs and 4717 from RCTs; 5278 for PCI, 8284 for CABG) evaluated incidence of MI. There was a significant higher incidence of MI in patients undergoing PCI compared with those re-vascularized by CABG (OR

1.22:1.11-1.35, p<0.00001). This result was substantially determined by NRCTs (OR 1.32:1.17-1.49, p<0.00001), whereas there was a non-significant trend favourable to CABG in RCTs (OR 1.12:0.97-1.29, p=0.14) **(see Figure 3 Panel B)** also excluding NOBLE study (**See Figure S2, web appendix).**

17 studies (6 RCTs and 11 NRCTs, total patients 14342, 4717 from RCTs and 9625 from NRCTS, 6509 for PCI, 7992 for CABG) were included for revascularization. The overall rate was significantly higher in PCI group (OR 1.52:1.34-1.72 p<0.00001) than in CABG group **(see Figure 3 C)**. This result was confirmed in both subgroups: OR 1.25:1.16-1.36 (p<0.01) for RCTs and OR 1.69:1.46-1.95 (p<0.01) for NRCTs. Similarly, PCI increased risk of TLR and ischemia-driven revascularization **(see Figure 4)**.

At meta-regression analysis, the use of two arterial graft or first generation DES correlated with the higher incidence of repeated revascularization with PCI (Beta 0.15 [0.12-0.18] and 0.2 [0.15-0.24] respectively for two arterial graft and use of I gen DES. Distal left main resulted not significant (Beta 0.08 [0.02-1.7], p 0.51), while use of IVUS was protective (Beta -0.02 [-0.09-:-0-01) **(see Figures 5 A-C).**

Regarding in hospital events, from the analysis of 10 studies (of whom 2 RCTs) PCI reduced risk of death (OR 0.70:0.57-0.86, p <0.01)], as well as stroke (OR 0.59 :0.38-0.93, p 0.02) **(see Figure S4, web appendix).**

Finally, 12 studies (4 RCTS) reported the incidence of stent thrombosis (Total patients 6542, 2208 from RCTs and 4334 from NRCTs) whereas 6 (3 RCTs) described rate of graft occlusion (3007 total patients, 1903 from RCTs, 1104 NRCTs). The analysis of this data showed a higher Incidence of graft occlusion compared to definite or probable stent thrombosis, respectively 3.24% (2.25-4.23) for graft occlusion and 2.13% (1.28-2.98) for

stent thrombosis **(see figure 6 A-B).** Specific outcomes definition and data on single study basis are described in supplementary appendix (see **Tables S5-S7, web appendix**)

Subgroup analysis for syntax score

5 studies evaluated (2 RCTs and 3 NRCTs, 2886 patients in PCI group, 4398 in CABG group) MACEs in patients with a Syntax score <22 showing similar outcomes between the two strategies (OR 1.15: 0.98-1.35, p =0.08).

2533 patients, 1087 in PCI group and 1446 in CABG group, with an intermediate syntax score (22-32) were analysed in 3 studies (2 RCTs). MACEs rate was higher in PCI group (OR 1.26:1.05-1.5, p = 0.01). An analogue result was obtained for patients with a Syntax score > 32, from a meta-analysis of 2 RCTs and 2 NRCTs including this high-risk population (total patients 6956; PCI 2766, CABG 4190) (OR 1.27: 1.19-1.36, p <0.0001). All these results did not changed removing NRCTs from the analysis.

3 studies (of which 2 RCTs) reported the incidence of death among patients with a syntax score <22. There was a non-significant higher incidence of all-cause death in patients treated with PCI (OR 1.43: 0.82-2.51, p =0.21). Only 1 RCT was available for intermediate syntax score (22-32), with higher risk for PCI (OR 1.28: 1.21-1.36, p <0.00001).

3 papers (2 RCTs) were included for high risk patients (Syntax >32) without difference (OR 1.04: 0.43-2.52, p 0.92, all CI 95%). For this subgroup, the exclusion of NRCTs from the analysis did not significantly change the result.

A subgroup analysis for syntax score was also performed for revascularization. 3 trials (2 RCTs involving 5351 patients, 2099 for PCI and 3252 for CABG) reported this endpoint for patients with syntax score < 22, resulting in a non-significant higher incidence of

revascularization for PCI group (OR 1.43. 0.82-2.51, p =0.21). Result reached statistical significance after excluding NRCT (OR 1.11: 1.08-1.14). More repeated revascularizations were also observed in patients with intermediate syntax score (OR 1.28: 1.21-1.36, p <0.00001. 1 RCT available) as well with syntax score >32 (OR 1.71: 1.55-1.89 p<0.0001, from 2 RCTs and 1 NRCT, **see figures S5, web appendix**).

DISCUSSION.

To the best of our knowledge this is the first meta-analysis including data from all RCTs comparing PCI vs CABG for ULMCA, along with data from observational studies with multivariate adjustment.

The main results were:

1- At a mean follow up of 5 years there were more MACEs with PCI strategy than CABG; this result is mainly driven by a higher incidence of repeated revascularization particularly in case of complex lesions (Syntax score >=22);

2- The difference in terms of repeated revascularization was more evident using first generation DES and for patients treated with two arterial conduits; while use of IVUS improved performance of PCI.

3- Stroke incidence and hospital death were higher with CABG strategy;

At a medium-long term follow up patients who underwent ULMCA revascularization with PCI showed a slight higher (10% increase) incidence of MACE. Even if MACE represented a widespread used composite endpoint in scientific community, thanks to its ability to reduce sample size needed by researchers, its heterogeneous definition generated important divergences in results interpretation (16). For example, the two recently published

RCTs on this theme, NOBLE and EXCEL trial (2,6), showed apparent discordance in terms of primary composite outcome that can probably be justified by the inclusion of revascularization in the first and the exclusion in second one. Focusing on single component outcome, our meta-analysis highlighted that while no significant differences emerged in terms of overall mortality, revascularizations were more frequent with PCI strategy both in randomized as in not randomized studies, while reduction of MI offered by CABG was evident only after adding observational studies. These results were substantially consistent with all previous published studies and meta-analysis (2,5) even if only Athappan et al. (17) evidenced a trend for more MI with PCI.

Correlation between lesion complexity and outcome has been confirmed by the present analysis. In the Syntax Score sub analysis, the statistical significance for need of new revascularization at follow up was achieved for Syntax Score >=22 with a subsequent clear linear correlation for incremental values. This report was well known since Syntax score publication (18) and clearly implemented in European and American guidelines indication (19,20). Similarly, our data demonstrated that in patients with low Syntax score rates of revascularization did not differ among PCI and CABG, while risk of death did not differed across the subgroups.

Specific revascularization techniques influenced the risk of subsequent revascularization. According to our meta-regression analysis the higher incidence of revascularization in PCI patients was more evident with the use of first generation DESs and when compared to those treated with two arterial grafts, while it was reduced by use of IVUS. The majority of studies considered in our meta-analysis used first generation DES. Last generation DESs, with their more biocompatible structure, have been shown to have the potentiality to decrease incidence of repeated revascularizations, stent thrombosis and

consequently MACEs in head-to-head comparison versus previous generation, even if mainly in other lesion settings (8, 21,22) with little evidence on LM treatment (23) and in terms of PCI vs CABG comparison (2,6). NOBLE and EXCEL trial compared Biolimus-Eluted Stent (BES) and fluoro-polymer-based cobalt–chromium everolimus-eluting stents (EES) respectively to CABG strategy. At a mean follow up of 5 and 3 years, patients in PCI cohorts needed more repeated revascularization and experience more non-procedural MI. Of note, a significant difference emerged only for total revascularization, while TLR were similar between the two groups. This findings confirmed a good outcome of PCI with new DESs on LM lesions, while the repeated revascularizations were probably due to CAD progression in other sites. More data with the use of new DESs are needed to clarify better these results. Moreover benefit of use of IVUS is largely known with DES (4,27), as a means to optimize procedural performance,resulting into improved long-term clinical outcomes. On the other hand the use of multiple arterial grafting seemed to increase CABG benefit in our analysis. This result is consistent with a very large amount of observational evidence (28).However, the recently published interim 5-year analysis of the ART trial (7) didn’t found any survival benefit with the use of bilateral mammary artery graft with a concomitant increase in wound complications. The lack of power to detect significant differences in hard outcomes at a 5 years follow up, the high rate of cross-over between groups, the use of the radial artery in almost 30% of the patients in the single mammary group and the exceptionally high compliance with optimal medical therapy can probably explain the negative results of this paper. It is reasonable to suppose that multiple arterial grafting, when technically feasible and specially in younger patients, could give a long term benefit compared to venous bypass plus single internal mammary artery and to PCI as suggested by our meta-analysis.

The higher incidence of stroke in CABG patients stressed the importance of a tailored approach for the choice between percutaneous and surgical revascularization. The present result confirmed those previously evidenced by several meta-analysis (17,29) and can probably be linked to the higher in-hospital-mortality with CABG emerged in our study. Consequently, when evaluating a patient with ULMD, the risk of in hospital complication according to single patient risk should be carefully weighed against that of subsequent revascularization, also according to Syntax Score.

LIMITATION:

Our study present many limitations. As results were analysed on an aggregate data basis, no assessment of between groups equal distribution of baseline characteristics was possible. As with any meta-analysis all included studies' limitations are shared by our work, the statistical heterogeneity among the studies included in the primary and secondary outcomes' analysis resulted always severe, while for publication bias funnel plot analysis showed that it was not relevant, as confirmed by not significant Egger's test (p 0.57; **see appendix, figure S1**). The Finally, some results show borderline statistical significance so that a larger sample size as well a longer follow-up could increase statistical reliability to the present results.

CONCLUSION:

CABG reduced risk of repeated revascularization compared to PCI in patients with ULMCA, especially for those with Syntax Score more than 22, with a higher risk of in hospital death. Use of double arterial grafts improved performance of CABG as well as Intra-coronary imaging did for PCI approach.

DISCLOSURES:

None.

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Figure Legend

Figure n 1 : Study Design and review's profile

Figure n 1 captation: 26 papers were finally selected for the systematic review and meta-analysis, 6 Randomized Controlled Trials (RCTs) and 20 observational studies with

multivariate adjustment or propensity score analysis (NRCTs) with a total of 19314 patients included in the analysis, of which 8501 treated with PCI and 10813 with CABG.

Figure n 2: Incidence of MACEs

Figure n 2 legend: MACE = Major adverse cardiovascular events

Figure n 2 captation : MACEs is meant in the present study as a composite of all-cause death, Myocardial Infarction, definite or probable stent thrombosis and target vessel revascularization. In the highest part of the figure are shown results coming from RCTs, in the middle results from multivariate adjusted clinical trials and in the lowest the combination of both. Global Odds ratio for MACE : OR 1.10, 95%CI 1.07-1.14, p <0.01

Figure n 3 A-C : Incidence of death (A), myocardial infarction (B) and revascularization (C)

Panel A captation : Incidence of death . In the highest part of the figure are shown results coming from RCTs, in the middle results from multivariate adjusted clinical trials and in the lowest the combination of both. Global Odds ratio for death: OR 0.94:0.89-1.00, p =0.05

Panel B captation: Incidence of myocardial infarction . In the highest part of the figure are shown results coming from RCTs, in the middle results from multivariate adjusted clinical trials and in the lowest the combination of both. Global Odds ratio for MI: OR 1.22:1.11-1.35, p<0.00001.

Panel C captation: Incidence of revascularization. In the highest part of the figure are shown results coming from RCTs, in the middle results from multivariate adjusted clinical trials and in the lowest the combination of both. Global Odds ratio for revascularization: OR 1.52:1.34-1.72 p<0.00001

Figure n 4 : Incidence of Target Lesion Revascularization (TLR) and ischemia-driven TLR.

Figure n 6 captation: Incidence of Target Lesion Revascularization (TLR) (above) and only ischemia-driven TLR (below). Global OR for TLR : 1.41: 1.06-1.88, p< 0.00001. Global OR for ischemia-driven TLR - 1.26:1.14-1.40, p>0.00001.

Figure n 5 a-c: Meta regression of two arterial grafts on revascularization (A); meta regression of first generation DES on revascularization (B); meta regression of IVUS on revascularization (C)

Panel A captation : Correlation between the use of two arterial graft and the incidence of revascularization . Beta 0.15 [0.12-0.18].

Panel B captation : Correlation between the use of first generation DES and the incidence of revascularization . Beta 0.2 [0.15-0.24]

Panel C captation : Benefit of IVUS use on incidence revascularization . Beta -0.02 [-0.09-:-0-01].

Figure n 6 : Incidence of stent thrombosis (A) and graft occlusion (B).

Panel A captation : Incidence of stent thrombosis. In the highest part of the figure are shown results coming from RCTs, in the middle results from multivariate adjusted clinical trials and in the lowest the combination of both. Global Odds ratio for stent thrombosis

Panel B captation : Incidence of graft occlusion. In the highest part of the figure are shown results coming from RCTs, in the middle results from multivariate adjusted clinical trials and in the lowest the combination of both.